COL1A1 gene

collagen type I alpha 1 chain

Normal Function

The *COL1A1* gene provides instructions for making part of a large molecule called type I collagen. Collagens are a family of proteins that strengthen and support many tissues in the body, including cartilage, bone, tendon, skin, and the white part of the eye (the sclera). Type I collagen is the most abundant form of collagen in the human body.

A component of type I collagen called the pro-α1(I) chain is produced from the *COL1A1* gene. Collagens begin as rope-like procollagen molecules that are each made up of three chains. Type I collagen is composed of two pro-α1(I) chains and one pro-α2(I) chain (which is produced from the *COL1A2* gene).

The triple-stranded procollagen molecules are processed by enzymes outside the cell to create mature collagen. The collagen molecules then arrange themselves into long, thin fibrils that form stable interactions (cross-links) with one another in the spaces between cells. The cross-links result in the formation of very strong type I collagen fibers.

Health Conditions Related to Genetic Changes

Caffey disease

A particular mutation in the *COL1A1* gene causes infantile cortical hyperostosis, commonly known as Caffey disease. The signs and symptoms of Caffey disease are usually apparent by the time an infant is 5 months old. This condition is characterized by swelling of soft tissues (muscles, for example), pain, and excessive new bone formation (hyperostosis). The bone abnormalities mainly affect the jawbone, collarbones (clavicles), and the shafts (diaphyses) of long bones in the arms and legs. For unknown reasons, the pain and swelling associated with Caffey disease typically go away within a few months. Through a normal process called bone remodeling, which replaces old bone tissue with new bone, the excess bone is usually reabsorbed by the body and undetectable on x-ray images by the age of 2.

The mutation that causes this condition occurs in one copy of the *COL1A1* gene in each cell. It alters a single protein building block (amino acid), replacing the amino acid arginine with the amino acid cysteine at protein position 836 (written as Arg836Cys or R836C). This mutation results in the production of type I collagen fibrils that are variable in size and shape, but it is unknown how these changes lead to the signs and symptoms of Caffey disease.

dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans, a rare type of cancer that causes a tumor in the deep layers of the skin, is characterized by a noninherited (somatic) mutation involving the *COL1A1* gene. Somatic mutations are acquired during a person's lifetime and present only in certain cells, in this case cells in the skin from which the cancer arises. Dermatofibrosarcoma protuberans is associated with a rearrangement (translocation) of genetic material between chromosomes 17 and 22. This translocation, written as t(17;22), fuses part of the *COL1A1* gene on chromosome 17 with part of a gene on chromosome 22 called *PDGFB*. This translocation is found on one or more extra chromosomes that can be either the normal linear shape or circular.

The fused *COL1A1-PDGFB* gene provides instructions for making a combined (fusion) protein that researchers believe ultimately functions like the active PDGFB protein. In the translocation, the *PDGFB* gene loses the part of its DNA that limits its activity, and production of the COL1A1-PDGFB fusion protein is controlled by *COL1A1* gene sequences. As a result, the gene fusion leads to the production of a larger amount of active PDGFB protein than normal. Active PDGFB protein signals for cell growth and division (proliferation) and maturation (differentiation). Excess PDGFB protein abnormally stimulates cells to proliferate and differentiate, leading to tumor formation in dermatofibrosarcoma protuberans.

Ehlers-Danlos syndrome

Several mutations in the *COL1A1* gene can cause a form of Ehlers-Danlos syndrome known as the arthrochalasia type. Ehlers-Danlos syndrome is a group of disorders that affect the connective tissues that support the skin, bones, blood vessels, and many other organs and tissues. The arthrochalasia type is characterized by an unusually large range of joint movement (hypermobility) and dislocations of both hips at birth. The genetic changes that cause this form of the disorder occur in one copy of the *COL1A1* gene in each cell and lead to the production of a pro-α1(I) chain that is missing a critical segment. The absence of this segment interferes with the assembly and processing of pro-α1(I) chains into mature type I collagen molecules. Tissues that are rich in type I collagen, such as the skin, bones, and tendons, are most affected by this change.

At least one mutation in the *COL1A1* gene has been shown to cause a form of Ehlers-Danlos syndrome with signs and symptoms similar to the classical type. Classical Ehlers-Danlos syndrome is characterized by skin that is soft, highly stretchy (elastic), and fragile; abnormal scarring; and joint hypermobility. Additionally, people with a *COL1A1* gene mutation are prone to tearing (rupture) of major arteries in adulthood. The mutation that causes this condition occurs in one copy of the gene in each cell. It changes one of the amino acids in the pro-α1(I) chain, replacing

the amino acid arginine with the amino acid cysteine at position 134 (written as Arg134Cys or R134C). The altered protein interferes with other collagen-building proteins, disrupting the structure of type I collagen fibrils and trapping collagen in the cell. Researchers believe that this *COL1A1* mutation only rarely underlies Ehlers-Danlos syndrome.

intervertebral disc disease

osteogenesis imperfecta

Osteogenesis imperfecta is the most common disorder caused by mutations in the *COL1A1* gene. People with this condition have bones that break easily, often from mild trauma or with no apparent cause. In addition, affected individuals can have a blue or grey tint to the part of the eye that is usually white (the sclera), short stature, hearing loss, respiratory problems, and a disorder of tooth development called dentinogenesis imperfecta. Hundreds of *COL1A1* gene mutations that cause osteogenesis imperfecta have been identified. Most of the mutations that are responsible for osteogenesis imperfecta type I, the mildest form of this disorder, reduce the production of pro-α1(I) chains. With fewer pro-α1(I) chains available, cells can make only half the normal amount of type I collagen. A shortage of this critical protein underlies the bone fragility and other characteristic features of osteogenesis imperfecta type I.

Several kinds of mutations in the *COL1A1* gene cause the more severe forms of osteogenesis imperfecta, including types II, III, and IV. Some of these mutations delete segments of DNA from the *COL1A1* gene, resulting in an abnormally shortened pro-α1(I) chain. Other genetic changes alter the sequence of amino acids in the pro-α1(I) chain, usually replacing the amino acid glycine with a different amino acid. In some cases, amino acid substitutions alter one end of the protein chain (called the C-terminus), which interferes with the assembly of collagen molecules. These *COL1A1* gene mutations lead to the production of abnormal versions of type I collagen. When this abnormal collagen is incorporated into developing bones and other connective tissues, it causes the serious health problems associated with severe forms of osteogenesis imperfecta.

other disorders

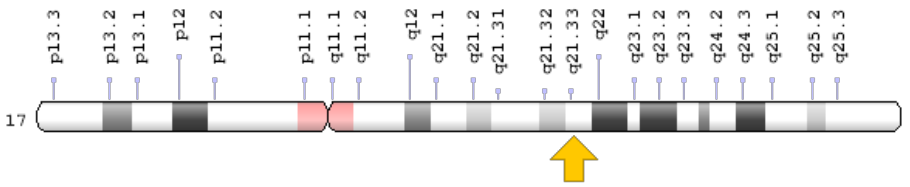
People with certain *COL1A1* mutations exhibit the signs and symptoms of both osteogenesis imperfecta and Ehlers-Danlos syndrome (described above). These mutations usually replace the amino acid glycine with a different amino acid in the pro-α1(I) chain, which interferes with the assembly and processing of pro-α1(I) chains into mature type I collagen molecules. The resulting abnormal type I collagen fibrils weaken connective tissue, causing the signs and symptoms associated with these two conditions.

A common variation in the *COL1A1* gene (called a polymorphism) appears to increase the risk of developing osteoporosis. Osteoporosis is a condition that makes bones progressively more brittle and prone to fracture. This polymorphism, which occurs in a regulatory region of the *COL1A1* gene, likely affects the production of type I collagen. Several studies have shown that women with this genetic change are more likely to have signs of osteoporosis, particularly low bone density and bone fractures, than are women without the change. This variation is only one of many factors that can increase the risk of osteoporosis.

Chromosomal Location

Cytogenetic Location: 17q21.33, which is the long (q) arm of chromosome 17 at position 21.33

Molecular Location: base pairs 50,184,096 to 50,201,648 on chromosome 17 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- alpha 1 type I collagen preproprotein
- CO1A1_HUMAN
- COL1A1 protein
- collagen I, alpha-1 polypeptide
- collagen of skin, tendon and bone, alpha-1 chain
- collagen type I alpha 1
- collagen, type I, alpha 1
- type I collagen alpha 1

Additional Information & Resources

Educational Resources

- Molecular Biology of the Cell (fourth edition, 2002): Collagens Are the Major Proteins of the Extracellular Matrix
  https://www.ncbi.nlm.nih.gov/books/NBK26810/#A3551
- Molecular Cell Biology (fourth edition, 2000): Collagen: The Fibrous Proteins of the Matrix
  https://www.ncbi.nlm.nih.gov/books/NBK21582/
- The Cell: A Molecular Approach (second edition, 2000): Collagen Fibrils (figure)
  https://www.ncbi.nlm.nih.gov/books/NBK9874/?rendertype=figure&id=A2050

GeneReviews

- Caffey Disease
  https://www.ncbi.nlm.nih.gov/books/NBK99168
- COL1A1/2-Related Osteogenesis Imperfecta
  https://www.ncbi.nlm.nih.gov/books/NBK1295

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28COL1A1%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D

OMIM

- COLLAGEN, TYPE I, ALPHA-1
  http://omim.org/entry/120150
- OSTEOPOROSIS
  http://omim.org/entry/166710

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/COL1A1ID186.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=COL1A1%5Bgene%5D
- Database of Human Type I and Type III Collagen Mutations
  http://www.le.ac.uk/genetics/collagen/
- HGNC Gene Family: Collagens
  http://www.genenames.org/cgi-bin/genefamilies/set/490

- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=2197
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/1277
- UniProt
  http://www.uniprot.org/uniprot/P02452

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